Sirolimus use in patients with subglottic stenosis in the context of granulomatous polyangiitis (GPA), suspected GPA and IgG4-related disease

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Abstract

Objective:

Subglottic stenosis is a severe, life-threatening disease found in immune-mediated diseases such as granulomatosis with polyangiitis (GPA) and in rare cases of IgG4-related disease. It can result in persistent airway compromise due to the fibrotic response following inflammation. Standard management involves repeated endoscopic interventions to dilate the airway, and occasionally requiring tracheostomy. In addition, immunosuppression remains a cornerstone of therapy aimed at controlling the underlying inflammatory disease, however, cumulative dosing leads to significant adverse effects. We present five cases of predominantly ANCA-negative GPA and a case of IgG4-related disease with subglottic stenosis in whom we evaluated the long term utility of sirolimus, which has beneficial anti-proliferative and fibrotic effects, in the management of these patients.

Methods:

We conducted a retrospective review of a cohort of patients with subglottic stenosis at a tertiary vasculitis unit. These patients were treated with sirolimus, in addition to conventional medical and endoscopic treatment. Clinical symptoms, frequency and time to endoscopic intervention pre- and post-treatment, additional rescue therapy, and any adverse effects were recorded and analysed.

Results:

Six patients were treated with sirolimus and have been followed for up to 9 years; two discontinued the drug due to adverse effects, early on. In the remaining four patients, glucocorticoids were withdrawn, and the frequency of endoscopic intervention was reduced. One patient on sirolimus required rituximab therapy for disease flare.

Conclusion:

Sirolimus may be a therapeutic option for some patients with severe subglottic stenosis allowing steroid withdrawal and resulting in a positive adverse effect profile.

Introduction

Subglottic stenosis is a potentially life-threatening manifestation of granulomatosis with polyangiitis (GPA) (1–3). Recurrent inflammation results in progressive fibrotic narrowing of the subglottis, manifesting as recurrent symptoms of respiratory distress and airway compromise.

The management of subglottic stenosis in these patients remains a major challenge due to the poor response to standard immunosuppressive therapy, need for repeated endoscopic intervention and in severe cases, open surgery and tracheostomy-dependence, although the need for latter measures has decreased with modern surgical airway approaches (4).

Sirolimus, a mammalian target of rapamycin (mTOR) inhibitor is widely used in organ transplantation and cancer chemotherapy, through its potent immunosuppressive and anti-proliferative effects (5). It inhibits fibroblast growth factor and platelet-derived growth factor-mediated smooth muscle proliferation, which result in anti-fibrotic effects (5). This principle has been widely applied in cardiology with the introduction of sirolimus-eluting coronary stents, and resultant reduction of stent restenosis (6). The combined immunosuppressive and anti-proliferative properties therefore identify sirolimus as a promising therapeutic strategy in patients with recurrent fibrotic subglottic disease. However, the potential for sirolimus-related pneumonitis may have deterred physicians from considering its use.

Two reports have described using rapamycin to maintain remission in relapsing or refractory GPA, however, longer term outcomes have yet to be described (7,8). Here, we report our centre’s experience of sirolimus in six patients with subglottic stenosis.

Materials and Methods

A retrospective analysis was conducted on six patients with subglottic stenosis at a tertiary vasculitis centre between 2001 to 2019. We included patients who received sirolimus treatment in addition to standard immunosuppressive therapy and endoscopic intervention.

Demographic, clinical, and laboratory data were extracted from medical records. The dose and duration of sirolimus in addition to previous medical treatment were recorded. ENT disease activity was assessed endoscopically. All vasculitis patients fulfilled the Watts criteria for GPA: [1]tracheal stenosis, [2]endoscopic/histological findings suggestive of vasculitis and/or positive anti-neutrophil cytoplasmic antibodies (ANCA) by indirect immunofluorescence where ELISA was unavailable, and [3]exclusion of other diagnoses; and all but one according to the American College of Rheumatology classification (9,10) (Supplemental Table 1). This was subdivided into limited and generalised GPA; where the former has respiratory and ENT-restricted disease.

Treatment outcomes were assessed based on clinical symptoms and endoscopic disease activity following the initiation of sirolimus. Outcome parameters included: clinical relapse rates, frequency and interval between endoscopic intervention pre- and post-treatment, need for rescue therapy and adverse effects. Remission was defined based on symptom reduction, and improved/stable endoscopic appearances. Statistical analysis was conducted using non-parametric Mann-Whitney-U test, with significance at $p<0.05$.

Results

Patient demographics

Baseline characteristics are summarised in Table 1 and 2. Six patients with subglottic stenosis were treated with sirolimus, five (83%) were female and the median age at presentation was 36 years (range:27-41). Four patients had limited GPA, one had systemic GPA (with skin, renal and lung involvement) and one patient was initially thought to have ENT-limited GPA, but was ultimately diagnosed with Immunoglobulin G4-related disease based on IgG4-positive immunostaining on subglottic biopsy (Supplemental Table 1).

The most common symptom was dyspnoea (n=6), followed by stridor (n=5) and dysphonia (n=3). Four patients had systemic manifestations of disease: arthralgia (n=2), haematuria (n=2), lung (n=2), and skin involvement (n=1). Two patients with GPA were ANCA-positive: c-ANCA with negative anti-proteinase-3 and anti-myeloperoxidase (MPO) antibodies (n=1), and p-ANCA with MPO autoantibody specificity (n=1). 3/5 cases were ANCA-negative, a typically underrepresented and difficult-to-study group.

Treatment

Indications for sirolimus were as follows: recurrent and severe disease requiring frequent dilatations despite standard immunosuppressive therapy (n=5) and refusal of rituximab or cyclophosphamide treatment (n=1). Four patients started sirolimus therapy while in remission, three of whom were on maintenance steroid treatment; while two patients flared prior to commencing treatment. The mean maintenance dose of sirolimus was 2mg (range:1-5mg). Previous immunosuppressive treatment is

summarised in Table 2: prednisolone (n=5), methotrexate (n=4), rituximab (n=3), cyclophosphamide (n=1), and azathioprine (n=1). The mean dose of prednisolone pre-sirolimus treatment was 9mg (range:5-20mg).

All six patients had regular diagnostic laryngoscopies and endoscopic interventions for SGS–these comprised: balloon dilatation (n=6), laser treatment (n=5), intra-lesional steroid injection (n=5), and sickle knife (n=1). Three patients required tracheostomies (of whom, two were successfully decannulated), while two patients required open reconstructive surgery for severe stenosis.

Outcomes

#1 and #4 stopped sirolimus due to side-effects at 2 and 4 months respectively, therefore were excluded from our analysis. The median duration from diagnosis of SGS to final follow-up was 9 years, and all patients had disease for at least two years prior to sirolimus initiation. Improvements in clinical symptoms and diagnostic laryngoscopy were achieved in the remaining four patients on sirolimus over a mean duration of 5 years. However all four relapsed when sirolimus was weaned or stopped completely (mean time-to-relapse was 6 months, range:4-8), necessitating the resumption of sirolimus. The mean sirolimus trough level was 6.5ng/ml (range:2.2–15.5) and dosage was adjusted to maintain levels of 5-9ng/ml.

Prednisolone was successfully stopped, and was reserved for the treatment of acute flares (Table 2). The mean daily dose of prednisolone during disease relapse was 10mg, which was weaned over a mean duration of 3 months (range:2-5 months). Three patients (#2, #4, #6) required rituximab rescue therapy for severe relapsing disease, one having discontinued sirolimus, and two despite ongoing sirolimus therapy. In case #6, two out of three rituximab doses were required while sirolimus

treatment was suboptimal and required up-titrating. The third infusion was necessitated when remission could not be achieved despite restarting sirolimus during a severe exacerbation having been off immunosuppression for nine months.

Endoscopic assessments of all six patients are shown in Table 3. Five patients had improved/stable endoscopic appearances. Those who remained on sirolimus beyond six months stopped prednisolone (median dose pre-sirolimus 6.25mg/day, post-sirolimus 0mg, p=0.06). There was a reduction in the mean number of endoscopic interventions (pre-sirolimus mean interventions/year=2.1, post-sirolimus=0.82, p=0.04), and an increased interval between dilatations (mean interval pre-sirolimus=6.6 months, post-sirolimus=20 months, p=NS) (Table 3).

Adverse effects

Two out of six patients experienced side effects (#1 had mouth ulcers, #4 had recurrent chest infections). None had severe complications except one who discontinued the medication (#4) requiring hospitalisation for infection. There were no significant differences between the pre- and post-sirolimus cholesterol and triglyceride levels (mean difference was 0.3 and 0.4mmol/L, respectively). No patient developed proteinuria or skin malignancies.

Discussion

We report a single centre series of six patients with subglottic stenosis treated with sirolimus, three of whom represents a unique and difficult-to-study group of ANCA-negative patients. The majority tolerated the drug and this resulted in stabilisation or improvement of disease, tapering of glucocorticoids (stopping in 3/5 patients), reduction in frequency of endoscopic interventions and a related increase in time between interventions. Relapse occurred over a mean duration of six months after the drug was discontinued in four patients, in keeping with the relapsing-and-remitting nature of ENT-GPA disease.

The management of subglottic stenosis is complex and requires a multi-disciplinary approach. Local therapy plays a significant part in the management with dilatation of strictures using laser or cutting balloons, intra-lesional steroid/mitomycin injections and occasionally tracheal reconstruction. Furthermore, to limit inflammation, which can lead to further stenotic areas, systemic immunotherapy is required. With relapsing disease, cumulative adverse effects are significant and therapy should be aimed at inducing remission of inflammation while minimising adverse effects. Historically, subglottic stenosis has been treated as severe ANCA-associated vasculitis with induction therapy using cyclophosphamide and glucocorticoids, followed by maintenance with azathioprine, methotrexate or mycophenolate mofetil and glucocorticoids. In resistant or relapsing cases, rituximab has recently replaced cyclophosphamide induction in some patients (1). However, cumulative adverse effects related to cyclophosphamide, glucocorticoids and rituximab for frequently relapsing disease means there is a clinical need for alternative therapies.

Sirolimus, an mTOR inhibitor is used in coated cardiac stents, renal transplantation, and the management of tuberous sclerosis. It has anti-fibrotic effects, and attenuates tracheal fibroblast metabolism, proliferation and collagen expression (11). Two reports of its use in patients with GPA were published over 10 years ago. The first demonstrated successful use in maintaining remission, in a patient with systemic and relapsing GPA with ENT involvement and skin malignancies, without significant adverse effects (7). The second suggested mixed efficacy in eight GPA patients with refractory and relapsing disease, only two of whom had subglottic stenosis. Seven out of eight patients had a decrease in the Birmingham Vasculitis Activity Score following six months of rapamycin, however, only three continued treatment beyond six months, having had a prolonged disease-free remission and prednisolone wean to less than 10mg/day (8). The remaining five patients discontinued sirolimus due to disease relapse, infectious or malignant complications.

Our data demonstrates that four out of six patients tolerated sirolimus without significant adverse events and have been able to use sirolimus as a steroid-sparing agent. Two out of the four patients required rituximab, one for nasal disease, and the other as rescue therapy for severe disease exacerbation after sirolimus was discontinued.

This series is limited by its small numbers. However, it suggests that in patients with subglottic stenosis, sirolimus therapy can enable glucocorticoid withdrawal and is associated with decreased need for endoscopic interventions. A larger trial of sirolimus

in patients with subglottic stenosis is warranted to better understand its benefits and limitations.

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Table 1: Baseline demographics

	N (%)
Number of patients	6
Female	5 (83)
Ethnicity	
Caucasian	3
Asian	2
Afro-Caribbean	1
Age at SGS presentation, *median* (IQR), *years*	36 (27-41)
Diagnosis, *N* (%)	
GPA (limited)	4 (66)
GPA (generalised)	1 (17)
IgG4-RD	1 (17)
Initial presentation	
Dyspnoea	6
Stridor/wheeze	5
Dysphonia	3
Nasal symptoms	2
Cough +/- haemoptysis	2
Ear symptoms	2
Constitutional	0
Extra-ENT manifestations	

Joint	2
Renal (including haematuria NOS)	2
Lung	2
Skin	1
ANCA	
PR3	0
MPO	1
Positive*	1
Negative	4
Tracheostomy	
No	3
Yes	3

Key

Positive* denotes ANCA positivity with negative MPO/PR3 antibodies.

SGS, subglottic stenosis; GPA, granulomatous with polyangiitis; IgG4-related disease, Immunoglobulin-G4 related disease; ENT, ear, nose and throat; ANCA, anti-neutrophil cytoplasmic antibody, PR3, anti-proteinase-3 antibody; MPO, anti-myeloperoxidase antibody, NOS, not otherwise specified.

Table 2: Clinical presentation and management of subglottic stenosis

No/Age/ Gender	Diagnosis	Presentation	ANCA positivity	Extra-ENT	Sirolimus		Medication pre-sirolimus	Rescue therapy post-sirolimus	Maintenance treatment at final follow-up	ENT management
					Dose	Duration				
1/26/F	GPA-L	Dyspnoea, stridor	Negative	Nil	2mg	2 months^	**Pred 8mg/day**, **MTX**, RTX (1)	Nil	Pred 5mg/day, AZA	Laser, intra-lesional steroid, balloon dilatation, sickle knife
2/55/F	GPA-L	Dyspnoea, Dysphonia, stridor, nasal crusting	Negative	Joint	5mg	>5 years	**Pred 20mg/day**, **MTX**, RTX (1)	HCQ, Pred 10mg/day^{+}, RTX (2)	Sirolimus	Laser, intra-lesional steroid, balloon dilatation, decrustation
3/16/F	IgG4-RD	Dyspnoea, Dysphonia	Negative	Lung nodule	2mg	>5 years	**Pred 7.5mg/day, AZA**, RTX (4)	Pred 10mg/day^{+}	Sirolimus	Laser, intra-lesional steroid, balloon dilatation, Tracheostomy (temporary), stent

										insertion/change, tracheal reconstruction
4/42/M	GPA-G	Dyspnoea, wheeze	c-ANCA*	Skin, renal, lung	1mg	4 months^	**Pred 5mg/day,** CYP (2), MTX	Pred 30mg/day, RTX (5)	Pred 5mg/day RTX	Intra-lesional steroid, cutting balloon dilatation, long term tracheostomy
5/31/F	GPA-L	Dyspnoea, wheeze, nasal, cough, hearing loss	p-ANCA (MPO)	Nil	2mg	>2 years	Nil	Pred 10mg/day^{+}	Sirolimus	Laser, intra-lesional steroid, balloon dilatation
6/41/F	GPA-L	Dyspnoea, stridor, hearing loss, cough, haemoptysis, aphonia	Negative	Joint	2mg	>4 years	Pred 5mg/day, **MTX**	RTX (3)	Sirolimus	Laser, balloon dilatation, tracheostomy (temporary)

Key

ANCA, anti-neutrophil cytoplasmic antibody; MPO, myeloperoxidase antibody; ENT, ear, nose and throat; Pred, prednisolone; MTX, methotrexate; AZA, azathioprine, RTX, rituximab; HCQ, Hydroxychloroquine; CYP, cyclophosphamide.

C-ANCA* indicates ANCA positivity with negative MPO/PR3 antibodies.

Maintenance treatment prior to starting sirolimus is highlighted in bold.

Extra-ENT denotes organ involvement other than those involving the ear, nose and throat. **Rescue therapy post-sirolimus** indicates any additional treatment required during disease flares, which were subsequently discontinued or withdrawn. **Maintenance treatment** indicates current immunosuppression at final follow-up. **Numbers in brackets** denote number of standard doses for each treatment.

^treatment discontinued due to adverse effects

[+]Prednisolone was added to treat acute flares and was weaned over a mean duration of 3 months (range: 2-5 months).

Table 3: Clinical and endoscopic assessments pre- and post-sirolimus treatment

Case	Pre-sirolimus				Post-sirolimus			
	Mean no. of relapse /year	**Mean no. of interventions /year**	**Mean interval between interventions (months)**	**Endoscopic appearance**	**Mean no. of relapse /year**	**Mean no. of interventions /year**	**Mean interval between interventions (months)**	**Endoscopic appearance**
1	2.0	2.0	6.0	Paradoxical vocal cord movement, recurrent granuloma and fibrosis requiring repeated laser/dilatation	1.3	1.5	11.4	Limited duration on sirolimus - Limited vocal cord abduction, minor inflammation, subglottic narrowing
2	3.0	4.0	4.5	Active tracheal disease requiring repeated dilatation	1.8	0.8	13.0	Improvement of tracheal disease, reduced/no inflammation, some crusting
3	3.5	1.8	4.5	Recurrent granulation tissue requiring repeated dilatation	0.4	0.8	-*	Improved appearances, occasional granulation, for routine stent change/clean only
4	2.7	1.7	7.6	Complete tracheal and bronchial stenosis,	3.0	2.3	7.0	Limited duration on sirolimus - Remains

				active subglottic disease				inflamed, marked granulomatous lesions/narrowing
5	0.5	1.0	16	Inflamed trachea/bronchus requiring dilatation, significant stenosis with fibrous band stricture proximal left main bronchus	0.7	0.7	25	Mild inflammation only, no new stenosis
6	0	1.5	1.5	Active on chronic inflammation, anterior subglottic stenosis	1.0	1.0	36	Grade 1 stenosis, not inflamed/erythematous, some stenosis, no signs of active disease

Key

SGS, subglottic stenosis

*only had two flares when sirolimus was weaned